## REMARKS

Applicants have amended their specification to reflect the issuance of U.S. Patent Nos. 6,503,905 and 6,586,431, from the grandparent and parent continuation applications, respectively, of the present application as requested in the outstanding Official Action.

All the claims submitted for examination in this application have been rejected on formal and/or substantive grounds. Applicants have amended their claims and respectfully submit that all the claims currently in this application are patentable over the rejection of record.

Turning to the objections of record, the first objection imposed in the outstanding Official Action is directed to Claims 18 and 19. These claims stand objected to, under 37 C.F.R. §1.75, as being duplicates of Claims 14 and 15, respectively.

Although applicants do not believe that the objected to claims are identical, they have, in a spirit of cooperation, cancelled Claim 15, thus retaining Claim 19, and Claim 18, thus retaining Claim 14. With this amendment, this objection has been made moot.

The second objection is made to Claims 15, 18 and 19, under 37 C.F.R. §1.75, as being a substantial duplicate of Claim 14. Insofar as Claims 15 and 18 have been cancelled, the sole issue in regard to this objection is whether Claim 14 is a substantial duplicate of Claim 19.

The distinction between Claims 14 and 19 resides in the concentrations of the active compound of Claim 1 in the pharmaceutical compositions recited in those claims. That is, the concentration of the compound of Claim 1 is an amount effective in treating each of the disorders recited in that claim. In Claim 19, on the other hand, the pharmaceutical composition requires an amount of the compound of Claim 1 required to provide an opioid

receptor binding modulating effective amount. As such, the concentration of the compound of Claim 1 required in Claim 14 is limited to specific concentrations required to treat the specific diseases recited in Claim 14. Claim 19, on the other hand, is a generic amount of the compound of Claim 1 that is effective in treating a generalized disorder or condition by providing an opioid receptor binding modulating effecting amount. The concentrations of the compounds of Claim 1 employed in the compositions of Claim 14 and 19 will thus not be the same. Therefore, the two claims are not identical.

The claims of the present application have been rejected on seven formal grounds. The first of these grounds is the rejection of Claim 1, under 35 U.S.C. §112, second paragraph, as being indefinite.

The specific basis for this ground of rejection involves the inclusion of preferable clauses. Suffice it to say, Claim 1 has been amended to remove these preferred indefiniteness-causing clauses.

The second formal ground of rejection is again directed to Claim 1 and is again imposed under 35 U.S.C. §112, second paragraph as being indefinite. In this ground of rejection, Claim 1 is rejected for the inclusion of phrases starting with the abbreviation "i.e."

This formal ground of rejection has also been made moot by the cancellation of the parenthesized phrase that begins with the term "i.e.,".

The aforementioned discussion of the first two formal grounds of rejection indicates that applicants have amended Claim 1. It is emphasized that a further change has been made to Claim 1 to correct a spelling error in the word "substituents."

The aforementioned amendment of Claim 1 deletes improperly recited limitations. It is emphasized, however, that new Claim 22, depend from Claim 1, reintroduces these

limitations. It is noted that the alkyl moieties in $R^1$, the ($C_1$-$C_8$)alkoxy substituent of $R^2$ and the alkyl moieties of $R^7$ and $R^8$ are recited, in new Claim 22, to be optionally substituted with one to four fluorine atoms. The deleted ?

The third formal ground of rejection is directed to Claims 14, 16, 18 and 20. These claims stand rejected, under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, these claims include narrower and wider ranges for the same limitations.

As indicated above, Claim 18 has been cancelled. As such, this third formal ground of rejection is directed to Claims 14, 16 and 20. These claims have been amended to delete the phrases that begin with the words "such as." Applicants submit that these deletions overcome the rejection of Claims 14, 16 and 20 under 35 U.S.C. §112, second paragraph.

Applicants have added new Claims 23 to 25 to reintroduce the deleted subject matter of Claims 14, 16 and 20, respectively.

The fourth formal ground of rejection is directed to Claim 4. Claim 4 stands rejected, under 35 U.S.C. §112, second paragraph, as being indefinite. The basis for this ground of rejection is the absence of a numbered claim upon which Claim 4 depends. Applicants have amended Claim 4 to identify Claim 1 as the claim from which Claim 4 depends.

The fifth formal ground of rejection, directed to Claims 17 and 21, is again imposed under 35 U.S.C. §112, second paragraph as being indefinite.

The indefiniteness of Claims 17 and 21 allegedly resides in the absence of any steps for determining how to identify "a disorder or condition, the treatment or prevention of which can be effected or facilitated by modulating binding to opioid receptors in a mammal."

The Official Action admits that diseases within the contemplation of this method of treatment are set forth in the specification. However, the Official Action argues that there is no disclosure in the specification describing how these diseases can be identified.

The issue raised in the fifth formal ground of rejection is outside the scope of the claims of the present invention. Determination of a disease that is amenable to treatment by modulating binding to opioid receptors is the province of one skilled in the art, e.g. a medical doctor. The present invention is directed to treatment of such diseases when a diagnosis of such a disease is made.

It is emphasized that enablement of a specification is predicated upon understanding by those skilled in the art. As stated above, those skilled in the art of the present invention are medical doctors and the like. Such skilled artisans are well aware of identification of the diseases recited in Claims 17 and 21. The specification, in the Background of the Invention section, sets forth a multiplicity of references which guide those skilled in the art to the relationship between the diseases indicated in the specification and the modulation of opioid receptor binding.

This ground of rejection implicitly denies, without contravening evidence, the learned publications identifying modulation of opioid receptor binding as having an effect upon the diseases mentioned in the specification. Applicants, therefore, challenge the examiner to present evidence establishing that the relationship between the diseases mentioned in the specification and modulation of opioid receptor binding is irrelevant to the effectuation of treatment of these diseases in mammals. In the absence of such evidence, applicants submit that the instant attack on the operability of the present invention of Claims 17 and 21 be rescinded.

The sixth formal ground of rejection is directed to Claims 14 to 21. Claims 14 to 21 stand rejected, under 35 U.S.C. §112, first paragraph, as not being enabled by the specification.

The Official Action avers that although the specification enables the claims directed to the method of treating pain, the specification does not provide enablement for the remaining claimed diseases.

To begin with, the state of the clinical arts in regard to δ-opioid receptor disease is more extensive than the applied Kowaluk et al., Annual Reports in Medicinal Chemistry (1998), wherein δ-opioid agonists are reported to be safe and effective analgesics. Attention is directed to the specification of the present application, at Page 1, lines 18-21, wherein it is recited that activation of δ-opioid receptors influence motility of the gastrointestinal tract. This additional use is set forth in the Burks (1995) article in "The Pharmacology of Opioid Peptides," edited by Tsang Harwood Academic Publish. As such, treatment of gastrointestinal disorders, such as gastritis, functional bowel disease, irritable bowl syndrome, functional diarrhea, functional distension, functional pain, nonulcerogenic dyspepsia and other disorders of motility and secretion and emesis are clearly known to those skilled in the art to be treatable by δ-opioid receptor inhibitors.

Although other diseases mentioned in Claims 14 to 21 are not illustrated in the specification as being amenable to treatment using a δ-opioid receptor, such absence does not constitute non-enablement. Claims 14 to 21 include many diseases for which enablement is established, as indicated above. That some of the diseases mentioned in these claims are not enabled, and may not be operative, does nothing to invalidate these claims. Even if some of the claimed combinations are inoperative, the claims are not necessarily invalid. It is not the

function of claims to specifically exclude possible inoperative embodiments. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984).

The seventh and final formal ground of rejection is directed to Claims 15, 19 and 21. Claims 15, 19 and 21 stand rejected, under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for specific diseases, does not reasonably provide enablement for preventing diseases.

Applicants need not discuss the lengthy arguments raised in the outstanding Official Action. Suffice it to say, this ground of rejection has been made moot by the cancellation of prevention as being part of the method of Claims 19 and 21. As indicated above, Claim 15 has been cancelled.

Three substantive grounds of rejection have been imposed in the outstanding Official Action. The first of these is directed to Claims 1 to 21. Claims 1 to 21 stand rejected, under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over Claims 1 to 8 of U.S. Patent 6,503,905.

Applicants note that the Official Action indicates that this ground of rejection may be overcome by the filing of a Terminal Disclaimer, in compliance with 37 C.F.R. §1.321(c), to overcome this ground of rejection. Applicants submit herewith a Terminal Disclaimer, executed by an attorney of record in this application, which limits the term of any patent that issues from this application to one which expires concurrently with the expiration of the '905 patent.

The second substantive ground of rejection is another rejection imposed the judicially created doctrine of obviousness-type double patenting. In this case, Claims 16, 17, 20 and 21 stand rejected, under this ground, over Claim 1 of U.S. Patent 6,586,431.

Again it is not necessary to review the basis for this ground of rejection. Suffice it to say, applicants, in accordance with the suggestion made in the outstanding Official Action, submit a Terminal Disclaimer herewith disclaiming the term of any patent issuing from the present application to the termination date of the aforementioned '431 patent.

The third substantive ground of rejection imposed in the outstanding Official Action is directed to Claims 1-3, 6, 16, 17, 20 and 21. These claims stand rejected, under 35 U.S.C. §102(b), as being anticipated by Kametani et al., Yakugaku Zasshi, 24(11), 1489-1490 (1974).

The Official Action submits that this reference, by its disclosure of compounds 6, 3a and 3b, anticipate formula (I) of Claim 1 when $R^1$ is hydrogen, benzyl or cyclopropylmethyl; Q is methylene; X is CH; $R^2$, $Z^1$ and $Z^2$ are hydrogen; and $R^3$ is hydroxyl.

Applicants have amended Claim 1, from which all the remaining claims subject to this ground of rejection depend, to delete hydrogen from the meanings of $R^2$. It is apparent that the compound noted by Formula 6 in Kametani et al. requires that $R^1$ in Formula I of Claim 1 of the present application be hydrogen in order for the compound of formula 6 in Kametani et al. to read on generic formula I of Claim 1. The deletion of this meaning removes Kametani et al. as an anticipating reference of any of the claims currently in this application.

The above amendment and remarks establishes the patentable nature of all the claims currently in this application. Notice of Allowance and passage to issue of these claims,

Claims 1-14, 16, 17 and 19-21, is therefore respectfully solicited.

Respectfully submitted,

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